

PRELIMINARY AND SHORT REPORTS

THE TREATMENT OF CUTANEOUS BLASTOMYCOSIS WITH PROPAMIDINE*

A PRELIMINARY REPORT

JAMES W. COLBERT, JR., M.D., MAURICE J. STRAUSS, M.D., AND
ROBERT H. GREEN, M.D.

The synthesis of propamidine† (4-4' diamidino-diphenoxypropane) was reported in 1942 by Ewins and his co-workers in the investigation of trypanocidal drugs (1). In 1943, the therapeutic activity of propamidine as a topical antiseptic against Gram positive cocci in chronic wound sepsis was demonstrated by Thrower and Valentine (2) and by other clinical investigators (3, 4, 5). In 1945, Elson reported the *in vitro* sensitivity of *Blastomyces dermatitidis* to propamidine (6). *B. dermatitidis* was completely inhibited by 3.75 micrograms of propamidine per cc. of yeast extract agar. Because of the marked *in vitro* sensitivity of *B. dermatitidis* and the absence of toxic symptoms in cases of wound sepsis treated with topical application of propamidine, therapeutic trial in cases of cutaneous blastomycosis seemed warranted.

It should be emphasized that, in spite of the lack of toxic symptoms reported, when propamidine is used in concentration of 0.1% as a local antiseptic, this drug and related aromatic diamidines produce general toxic effects when given systemically. After the intravenous injection of 2 mgm. of propamidine per kg. of body weight in the treatment of African sleeping sickness, Lourie (7) noted the production of immediate and severe collapse which was alarming but transitory. Late toxic effects have also have been reported with the use of the aromatic diamidines. Delayed kidney and liver damage and dissociated anesthesia of the trigeminal nerve have been particularly serious. An excellent review of these compounds has been published recently by Schoenbach and Greenspan (8).

CASE HISTORY

The patient is a 25-year-old white man who first noticed a skin lesion on the left shoulder three years before admission. The lesion had begun as an erythematous papule which spread radially until the skin overlying the entire left supraclavicular area, left upper anterior chest, and left upper posterior chest was involved. Fifteen months before admission the diagnosis of cutaneous blastomycosis was made by one of the authors (M. S.). This diagnosis was confirmed by culture and biopsy. Chest x-ray and blastomycin skin test were both negative, and therapy with Lugol's solution was instituted and maintained for five months without significant improvement. Therapy was interrupted because of annoying epiphora, which ceased with discontinuance of the drug. Eight months before admission, a course of x-ray therapy was given and resulted in pronounced healing of the lateral and central portions of the lesion. However, the medial, anterior, and posterior edges continued to advance, and seven months after the last x-ray treatment the patient was admitted to the hospital for re-evaluation and therapy.

In vitro sensitivity

B. dermatitidis was isolated from the advancing edge and then subcultured on Sabouraud's dextrose agar. The subculture was then used for *in vitro* sensitivity determina-

* From the Department of Internal Medicine and the Division of Dermatology of the Yale University School of Medicine.

This investigation was aided by the Thomas B. Enders Fund.

Received for publication July 1, 1949.

† Propamidine used in this investigation was generously donated by Dr. W. O. Elson of the Research Laboratories of the Bauer and Black Division of The Kendall Company.

tions. Propamidine was incorporated into Sabouraud's dextrose agar in double dilutions from 0.62 mgm./20 cc. of agar to 0.018 mg./20 cc. of agar. The organism was then streaked on the plates, which were read after eighteen days at room temperature. Complete inhibition was present at a concentration of 7.5 micrograms of propamidine per cc. of agar.

Clinical application

Before institution of therapy, chest x-ray and blastomycin skin test were repeated and again found to be negative.

Propamidine was incorporated into 9% methyl cellulose gel to a concentration of 0.1%. This concentration of propamidine is that recommended by Thrower and Valentine (2) for treating wound sepsis, and, when applied locally in this concentration, no systemic toxicity resulted. Dressings were done daily and in the following manner: the lesion was cleansed with saline. A culture was taken by expressing pus from the elevated edge and streaking it on a blood agar plate incubated at 37°C. and on Sabouraud's dextrose agar incubated at room temperature. Propamidine gel was then applied to the surface of the lesion with a sterile tongue depressor; vaseline gauze was placed over the gel, a sterile dry gauze was applied, and the entire dressing was covered with a sterile towel. After nine days the patient was discharged and followed as an outpatient. Six weeks after completion of the first course of treatment, a second similar course was given.

RESULTS

Two cultures were done before beginning treatment. One culture, taken three weeks before therapy, was positive for *B. dermatitidis*. The other culture, taken the day before therapy, was negative for *B. dermatitidis*. Twenty cultures done during the first and second courses of treatment were negative. However, a culture taken 2 weeks after completion of the second course of therapy was positive for *B. dermatitidis*.

Clinically, the lesion has improved coincidentally with the application of propamidine. The elevated margin has flattened considerably, although complete healing has not occurred. Epithelialization has advanced, especially over the more superficial areas. The antero-medial edge, which is the point of maximum involvement, has improved, but at present it shows less improvement than other areas, perhaps because the depth of tissue involved renders topical application less efficacious. Tenderness has subsided over almost the entire edge except for the afore-mentioned antero-medial area.

No evidence of systemic toxicity has been noted either by clinical observation or by pertinent laboratory procedures. However, the patient complained of pruritus locally and, nine days after the onset of the first course of treatment, noted a burning sensation of the skin surrounding the lesion. Irritation of the skin edges was reported by Thrower and Valentine (2), and because of this irritation the maximum period recommended for a single course of treatment was ten successive days.

SUMMARY

The treatment of a case of cutaneous blastomycosis with propamidine is reported. Although complete healing has not occurred, a suggestively favorable clinical response has been noted. It is realized that further treatment is necessary before any definitive statement can be made. However, because of the prolonged follow-up required, the lack of other cases available, and the suggestive clinical response, a preliminary report appeared worth while.

REFERENCES

1. ASHLEY, J. N., BARBER, H. J., EWINS, A. J., NEWBERRY, G., AND SELF, A. D.: Chemotherapeutic comparison of the trypanocidal action of some aromatic diamidines. J. Chem. Soc., Part I, Vol. 20: 103-116, February, 1942.
2. THROWER, W. R., AND VALENTINE, F. C. O.: Propamidine in chronic wound sepsis. Lancet, 1: 133-136, January 30, 1943.

3. McINDOE, A. H., AND TILLEY, A. R.: Propamidine in chronic streptococcal infection of raw surfaces. *Lancet*, **1**: 136-138, January 30, 1943.
4. MORELY, G. H., AND BENTLEY, J. P.: Propamidine in burns. *Lancet*, **1**: 138-140, January 30, 1943.
5. KOHN, F., HALL, M. H., AND CROSS, C. D.: Propamidine at an EMS Hospital. *Lancet*, **1**: 140-142, January 30, 1943.
6. ELSON, W. O.: The antibacterial and fungistatic properties of propamidine. *J. Infect. Dis.*, **76**: 193-197, May-June, 1945.
7. LOURIE, E. M.: Treatment of sleeping sickness in Sierra Leone. *Ann. Trop. Med. and Parasitology*, **36**: 113-131, September, 1942.
8. SCHOENBACH, E. B., AND GREENSPAN, E. M.: The pharmacology, mode of action and therapeutic potentialities of stilbamidine, pentamidine, and other aromatic diamidines. A review. *Medicine*, **27**: 327-377, September, 1948.